

**REMARKS**

Applicants wish to thank Examiner Dutt and Examiner Chernyshev for the courtesies extended during the telephone conversation on January 17, 2007. The rejected claims 2-8 and 21 were discussed with respect to the comments made by the Examiner in the Advisory Action dated December 31, 2008. Although the rejections directed to these claims were not resolved, Examiners Chernyshev and Dutt provided helpful guidelines and suggested how the rejection under 35 U.S.C. 102(b) over Zhao, et al. (*PNAS*, 100: 2426-2431, 2003) might be addressed. Specifically, the Examiner has suggested to incorporate a process step of how MOMC cells are prepared, such as recited in former claim 21, *e.g.*, “wherein said monocyte is obtained by culturing peripheral blood mononuclear cells (PBMCs) *in vitro* on fibronectin, and collecting fibroblast-like cells expressing CD14 and CD34”. The Examiner has also requested an official submission of the Seta et al. publication (*Keio J Med* 56(2):41-47, 2007) to further demonstrate the distinction between the claimed MOMC cells and PSC cells of Zhao, et al.

Furthermore, the Examiner’s comments pertaining to the phrase “is able to” were discussed. While the Examiner still maintains that such recitation potentially raises issued under 35 U.S.C. §112, second paragraph, applicants have respectfully replaced the phrase with “capable of differentiating.” Since, MPEP 2173.05(g) states:

It was held that the limitation used to define a radical on a chemical compound as "incapable of forming a dye with said oxidizing developing agent" although functional, was perfectly acceptable because it set definite boundaries on the patent protection sought. *In re Barr*, 444 F.2d 588, 170 USPQ 33 (CCPA 1971) (emphasis added),

applicants contend that the ability to differentiate, *i.e.*, “capable” or “incapable” is acceptable under the MPEP guidelines because the phrase sets definite boundaries on the patent protection sought and is not vague and indefinite.

Applicants believe that in view of this paper, the application is in condition for allowance. Reconsideration and withdrawal of the pending rejections are respectfully requested.

#### Claim Status

Claims 2-16 and 19-22 are pending after entry of this paper. Claims 2-8 have been rejected. Claims 9-16, 19-20 and 22 have been withdrawn and claims 1, 17-18 and 21 have been cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a continuing application. Claims 2-8 have been amended.

Claim 2 has been amended to incorporate the subject matter of claim 21 and partially incorporate the subject matter of claims 3 and 4. Support may be found throughout the instant specification and previously presented claims.

Claim 2, 3 and 5-8 have been amended to replace the phrase “is able to differentiate” with a phrase “is capable of differentiating.”

Claim 4 has been amended to delete the phrase “osteoblasts, skeletal myoblasts, chondrocytes or.”

Claim 6 has been amended to replace the term “nerve” with the term “neurons” based on the Examiner’s suggestion (Office Action – page 3).

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Rejections under 35 U.S.C. §102

Claims 1-8 have been rejected under 35 U.S.C. §102(b) as being anticipated by Zhao, et al. (*PNAS*, 100: 2426-2431, 2003). Specifically, the Examiner contends that Zhao allegedly discloses the isolation of pluripotent stem cells (PSC) from human peripheral blood monocytes that resemble fibroblasts and express the monocytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45, and the presence of collagen type I would thus be inherent (Office Action – page 4). Furthermore, according to the Examiner, the He et al. (*Stem Cells* 25:69-77, 2007) publication allegedly discloses that MOMC exhibit similar morphology to fibrocytes and share similar surface markers as the fibrocytes, while concluding that such a disclosure supports that “MOMC are morphologically and phenotypically identical to the PSC of Zhao et al.” (par. bridging pages 4 and 5 of the Office Action). The Examiner further contends that Zhao allegedly discloses that human peripheral blood cells containing monocytes when cultured under specific conditions, differentiate into macrophages, lymphocytes, epithelial cells, neuronal cells, endothelial cells and hepatocytes (Office Action – page 5). Therefore, the Examiner maintains that Zhao allegedly anticipates the claimed invention and the burden to prove that inherency is not involved falls on the applicants (Office Action – page 6). Applicants respectfully disagree.

As an initial matter, applicants respectfully wish to remind the Examiner that there is a clear distinction between the terms “identical” and “similar,” which are not the same or equivalent. Thus, the reference to He, et al. for supporting the statement “MOMC are morphologically and phenotypically identical to the PSC of Zhao et al.” has no basis. In fact, the He, et al. publication merely states that a PSC cell population is very similar to the MOMC both in morphology and in phenotype (page 73, paragraph bridging columns 1 and 2). As the

Examiner well aware, in the field of molecular biology, being similar has nothing to do with being identical. Many cells are morphologically and phenotypically similar. Therefore, the Examiner has used improper hindsight to arrive at the conclusion that the claimed cells are identical to the PSC cells of Zhao.

However, in order to expedite prosecution and without disclaimer of or prejudice to the subject matter recited therein, applicants have amended claim 2 to partially incorporate the subject matter of claims 3 and 4 by reciting “wherein the cell is capable of differentiating into osteoblasts, skeletal myoblasts or chondrocytes” and the subject matter of claim 21 by reciting “the monocyte is obtained by culturing peripheral blood mononuclear cells (PBMCs) in vitro on fibronectin, and collecting fibroblast-like cells expressing CD14 and CD34” as suggested by the Examiner during an Interview held on January 17, 2008. In addition, applicants submit herewith a declaration under 37 CFR §1.132 by Dr. Masataka Kuwana (one of the inventors) and a review article published in a peer-reviewed journal entitled “Monocytes as potential progenitors” by Seta et al. (*Keio J Med* 56(2):41-47, 2007). Both readily demonstrate the differences between the presently claimed MOMC cells and PSC cells of Zhao.

Specifically, the declaration discloses:

- (1) results of experiments to culture MOMC under differentiation inducing conditions of PSC (paragraph 7), and
- (2) results of confirmation experiments of the method of Zhao, et al. (paragraph 8).

The results of the experiments (1) described in paragraph 7 of the declaration clearly show that MOMCs cultured under differentiation inducing conditions of Zhao, et al. do not differentiate into neuronal cells, epithelial cells or hepatocytes. On the other hand, PSCs under the conditions of Zhao et al. as described are able to differentiate into neuronal cells,

epithelial cells or hepatocytes. Thus, one skilled in the art would not and could not consider that MOMCs of the instant invention are the same as the PSCs of Zhao, et al.

Furthermore, as described in the attached declaration, Dr. Kuwana attempted to prepare the PSCs using the method disclosed by Zhao, et al. However, the resultant “cells morphologically resembling fibroblasts” do not show all of the characteristics described in the Zhao, et al. reference, which cast doubt on the reproducibility of the method of Zhao, et al. Moreover, these “cells morphologically resembling fibroblasts” prepared by the method of Zhao, et al. do not differentiate into osteoblasts, skeletal myoblasts or chondrocytes under the differentiation inducing conditions of MOMC set forth in the instant application (see Example 22 of the specification). Therefore, these results would imply to one skilled in the art that PSCs of Zhao, et al. cannot differentiate into osteoblasts, skeletal myoblasts or chondrocytes.

In light of these experimental results, the inventor’s declaration, the review article published in the peer-reviewed journal, and the amendments to the claims, applicants respectfully assert that the PSCs cannot differentiate into “osteoblasts, skeletal myoblasts or chondrocytes” as claimed herein and are not obtained by “culturing peripheral blood mononuclear cells (PBMCs) *in vitro* on fibronectin, and collecting fibroblast-like cells expressing CD14 and CD34.” Furthermore, the MOMCs cultured under the differentiation inducing conditions of Zhao, et al., as discussed in the declaration, do not differentiate into neuronal cells, epithelial cells or hepatocytes, whereas, the PSCs do. Hence, the claimed MOMCs are not anticipated by the PSC of Zhao, et al. expressly or inherently because Zhao does not disclose each and every element of the claims as presented herewith. Reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) of claims 1-8 as being anticipated by Zhao, et al. are respectfully requested.

Response to Rejections under 35 U.S.C. §103

Claim 21 has been rejected under 35 U.S.C. §103(a) as being unpatentable over Zhao, et al. (*PNAS* 100: 2426-2431, 2003) in view of Pujol, et al. (*Differentiation* 65: 287-300, 2000). Specifically, the Examiner contends that Zhao allegedly discloses the pluripotent stem cells expressing CD14, CD34 and CD45 that are obtained by culturing peripheral blood mononuclear cells. The Examiner attempts to reach the claimed invention by combining the teachings of Zhao, et al. and Pujol, et al. According to the Examiner, Pujol allegedly teaches culturing CD14 monocytes derived from PBMC on fibronectin-coated tissue culture plates (page 288, “Cell Culture”) and one skilled in the art would be motivated to combine the teachings from the two publications to arrive at the claimed invention disclosed in claim 21. Applicants respectfully disagree.

However, claim 21 has been cancelled without prejudice. Thus, this rejection is now moot.

Moreover, contrary to the Examiner’s contention, Zhao does not disclose the MOMCs of the instant invention as supported by the arguments above. Nor does Pujol overcome the shortcomings of Zhao, since one skilled in the art would necessarily have to perform a great deal of undue experimentation in order to possibly arrive at the claimed invention. For instance, differentiation of the PSC cells from monocytes requires growth factors such as macrophage colony-stimulating growth factor (M-CSF), whereas the Endothelial Like Cells (ELC) of Pujol even though produced on the fibronectin-coated tissue culture slides, still require M-CSF (page 288, column 2; lines 4-6 of Pujol) and other endothelial cell (EC) factors present in the EGM-2 medium (methods section of Pujol). Therefore, *arguendo*, if one skilled in

the art were to substitute the differentiation conditions of Zhao with those conditions used in Pujol, the skilled artisan would still not arrive at the claimed invention, because M-CSF factor is still used and since MOMC differentiation would not occur on fibronectin-coated slides without the presence of soluble factors produced by CD14<sup>+</sup> cells (Table 1 of Seta). Therefore, neither the combination of, nor Zhao, et al. and Pujol, et al. alone, suggests the claimed elements such as the monocyte-derived multipotent cells (MOMC) expressing CD14, CD34, CD45 and type I collagen, which are capable of differentiating into osteoblasts, skeletal myoblasts or chondrocytes, where such cells are obtained by culturing peripheral blood mononuclear cells (PBMCs) *in vitro* on fibronectin, and collecting fibroblast-like cells expressing CD14 and CD34. Pujol does not remedy the deficiencies in the monocyte derived cells (PSC) of Zhao, et al. Therefore, the combination of Zhao, et al. and Pujol, et al. does not make obvious the claimed invention. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §103(a) rejection of claim 21 as incorporated subject matter in claim 2 in view of the aforementioned remarks and amendments to the claims.

#### Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim 2 from which all of the dependent claims 3-8 and 21 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

### **CONCLUSION**

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

**AUTHORIZATION**

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4036.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4036.

Respectfully submitted,  
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